Synthesis of thiodisaccharides by photoinduced hydrothiolation of 2-acetoxy glycals

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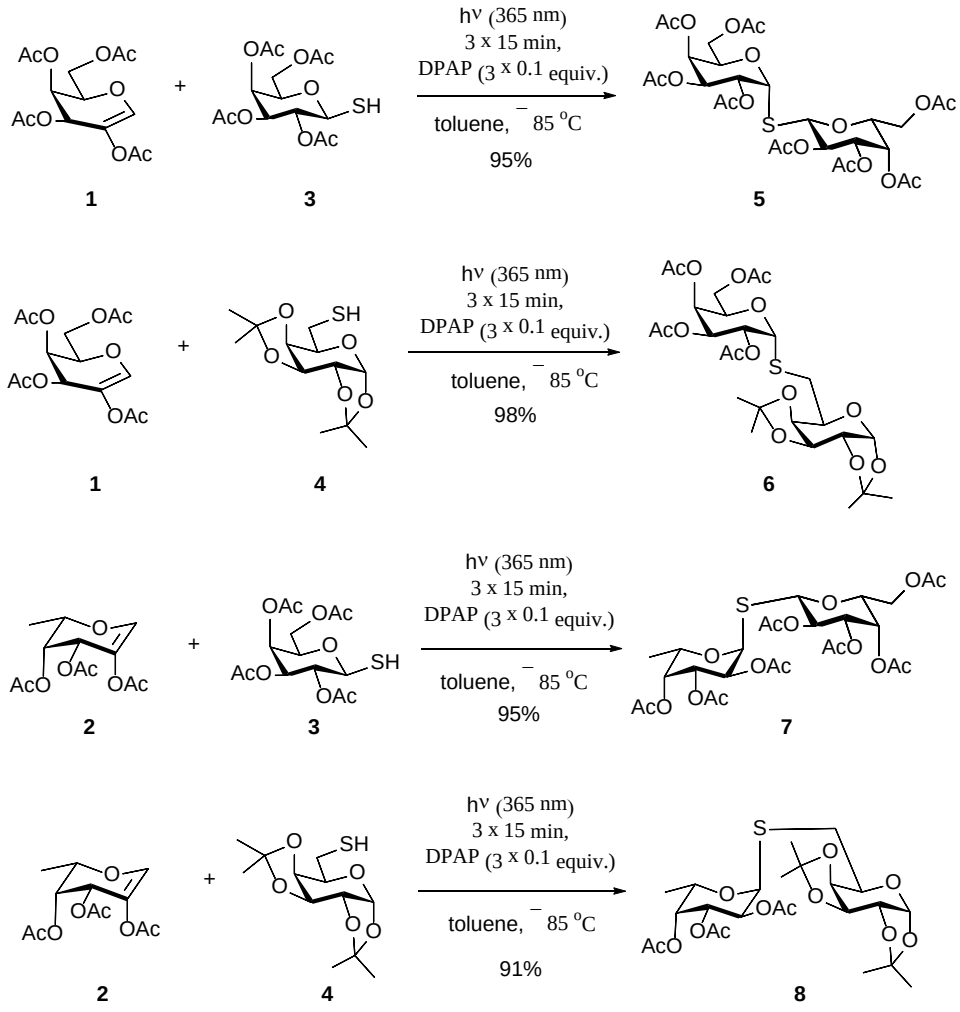

Glycomimetics are useful tools for studying biological processes and often serve as lead compounds for drug design.[1] Thiodisaccharides in which the interglycosidic oxygen is replaced by a sulfur atom are among the most important carbohydrate mimetics because of their resistance to enzymatic hydrolysis and their close similarity to the natural *O*-linked counterparts.[2]

A variety of methods are employed for synthesis of the thiodisaccharides[3] including glycosylation of thio acceptors with activated glycosyldonors,[4] S_N2-like displacement of a good leaving group of glycosyl acceptors with 1-thioaldoses,[5] Michael addition of 1-thiolates to sugar

enones,[6] Ferrier reactions between glycals and sulfur-containing coupling partners[7] and ring-opening of sugar epoxides[8] or thiiranes[9] by a 1-thioaldose nucleophile. Recently, it has been demonstrated that the efficient formation of thiodisaccharides is possible by photoinduced free-radical addition of sugar thiols to unsaturated carbohydrates bearing an exo-[10,11] or endocyclic[12,13] double bond. Due to the mild reaction conditions, high yields, complete regioselectivity and tolerance to a wide range of functional groups, these radical–mediated thiol-ene coupling reactions[14] are ideally suited to the preparation of thiodisaccharides and other *S*-linked glycoconjugates.[15]

We have shown that photoinduced hydrothiolation of 2-acetoxy-D-glucal with various sugar thiols gave 1,2-*cis*-α-*S*-disaccharides with full regio- and stereoselectivity in good to excellent yields.[12] Here, we present the synthesis of α-D-galactopyranosyl and α-L-fucopyranosyl thiodisaccharides **5-8** by the photoinitiated thiol-ene reactions of 2-acetoxy-3,4,6-tri-*O*-acetyl-D-galactal **1**[16] and 2-acetoxy-3,4-di-*O*-acetyl-L-fucal **2**[17] with thiols **3**[18] and **4**.[19]

The thiol additions were carried out with a 1.3:1 thiol:ene ratio in toluene by irradiation at λ_{max} 365 nm for 3 x 15 min in the presence of 2,2-dimethoxy-2-phenylacetophenone (DPAP, 3 x 0.1 equiv) as the photoinitiator. Unexpectedly, our initial experiments with thiol **3** at room temperature showed only moderate conversion of the starting glycal derivatives, and the isolated yields of thiodisaccharides were disappointingly low (42% for **5** and 33% for **7**). Applying higher excess of thiol or longer exposure to UV light only resulted in a very slight increase of the conversion. Studiyng the temperature effect, we have found that the conversion of the glycals can substantially be improved by cooling. Significant increase of the conversion was observed at -40 °C and complete conversion occurred if the reaction mixture was cooled to -80 or -90 °C.

Therefore, all reactions were carried out at -85 ºC and the thiodisaccharides **5**-**8** could be isolated in excellent yields.

Experimental

General Methods.

2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-*lyxo*-hex-1-enitol (**1**),[16] 2,3,4,-tri-*O*-acetyl-1,5-anhydro-6-deoxy-L-*lyxo*-hex-1-enitol (**2**),[17] 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranose (**3**),[18] and 1,2:3,4-di-*O*-isopropylidene-6-deoxy-6-thio-α-D-galactopyranose (**4**)[19] were prepared according to literature procedures, 2,2-dimethoxy-2-phenylacetophenone (DPAP) was purchased from Sigma Aldrich Chemical Co. Optical rotations were measured at room temperature with a Perkin-Elmer 241 automatic polarimeter. TLC was performed on Kieselgel 60 F254 (Merck) with detection by immersing plates into 5% ethanolic sulfuric acid followed by heating. Column chromatography was performed on Silica gel 60 (Merck 0.063-0.200 mm). Solutions in organic solvents were dried over $MgSO_4$, and concentrated in vacuum. The ^1H (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded with Bruker DRX-400 spectrometer. Chemical shifts are referenced to Me_4Si (0.00 ppm for ^1H) and to the residual solvent signals ($CDCl_3$: 77.00 ppm for ^{13}C). The coupling constant values (*J*) are given in Hz.

The photocatalytic reactions were carried out in a borosilicate vessel by irradiation with a Hg-lamp giving maximum emission at 365 nm. The set-up consisted from the reaction vessel and the cooling medium (acetone–liquid nitrogen mixture in our case) in a Dewar flask UV-lamp placed next to the mixture (Figure 1). The entire set-up was covered by an aluminium foil tent. Before irradiation, the reaction mixture was cooled to –85°C.

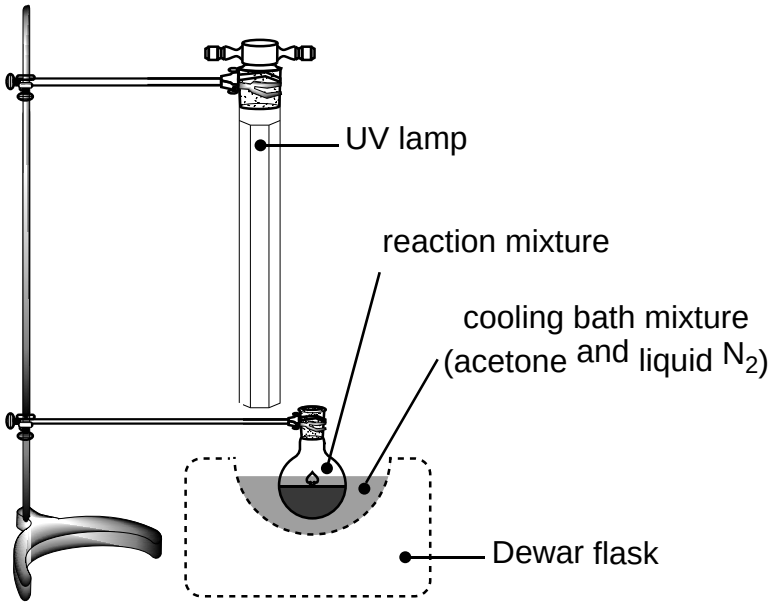

Figure 1. The experimental setup for irradiation at low temperature (the aluminum foil tent/shield, recommended only to protect the laboratory personnel, is not shown)

(2,3,4,6-Tetra-*O*-acetyl-α-D-glalactopyranosyl)-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (5). 2-Acetoxy-D-galactal derivative **1** (165 mg, 0.50 mmol), thiol **3** (219 mg, 0.60 mmol, 1.2 equiv.) and 2,2-dimethoxy-2-phenylacetophenone (DPAP) (13 mg, 0.05 mmol, 0.1 equiv.) were dissolved in toluene (4 ml). The reaction mixture was cooled to −85°C and irradiated with UV light. After 15 min DPAP (13 mg, 0.05 mmol, 0.1 equiv.) dissolved in toluene (0.5 ml) was added. The mixture was cooled to −85°C and irradiated with UV light for another 15 min. Another portion of DPAP (13 mg, 0.05 mmol, 0.1 equiv.) in toluene (0.5 ml) was added and the irradiation at –85°C continued for another 15 min. When TLC showed complete conversion (*n*-hexane : EtOAc = 1:1 v/v) the mixture was concentrated and chromatography (55:45 *n*-hexane–EtOAc, 50 g silica gel) gave 329 mg (95%) of **5** as a white foam. R_f 0.3 (1:1 *n*-hexane–EtOAc), $[\alpha]_D$= +128.8 (c = 0.1, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$)

δ 6.00 (d, *J* = 5.0 Hz, 1H), 5.46 (d, *J* = 1.8 Hz, 1H), 5.42 (d, *J* = 3.1 Hz, 1H), 5.29-5.16 (m, 3H), 5.04 (dd, *J* = 10.0, 3.3 Hz, 1H), 4.59 (d, *J* = 10.0 Hz, 2H), 4.20-4.05 (m, 4H), 3.99 (t, *J* = 6.4 Hz, 1H), 2.17, 2.15, 2.05, 2.05, 2.04, 2.04, 1.99, 1.98 (8 x s, 8 x C*H*$_3$, 24H).^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 170.1, 170.0, 169.9, 169.9, 169.6, 169.1 (8C, 8 x *C*O), 82.8, 82.5, 74.7, 71.7, 68.3, 67.9, 67.8, 67.2, 67.2, 67.0 (10C, skeleton carbons), 61.5, 60.3 (C-6, C-6'), 20.5, 20.5, 20.5, 20.5 (8C, 8 x *C*H_3). Anal. Calcd. for $C_{28}H_{38}O_{18}S$: C, 48.41; H, 5.51; S, 4.62. Found C, 49.91; H, 5.33; S, 4.66.

1,2:3,4-Di-*O*-isopropylidene-6-*S*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-6-thio-α-D-galactopyranose (6). 2-Acetoxy-D-galactal derivative **1** (220 mg, 0.665 mmol), thiol **4** (220 mg, 0.796 mmol, 1.2 equiv.) and DPAP (17 mg, 0.066 mmol, 0.1 equiv.) were dissolved in toluene (5 ml). The reaction mixture was cooled to −85°C and irradiated with UV light. After 15 min, a solution of DPAP (17 mg, 0.066 mmol, 0.1 equiv.) in toluene (0.5 ml) was added and the irradiation at −85°C was continued for another 15 min. The last operation was repeated one more time. When TLC showed complete conversion (95:5 CH_2Cl_2–acetone) the mixture was concentrated and chromatography (97:3 →95:5 CH_2Cl_2–acetone, 53 g silica gel) gave 398 mg (98%) of **6** as white foam. R_f 0.4 (95:5 CH_2Cl_2_acetone), $[\alpha]_D$ = +89.4 (c = 0.5, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (d, *J* = 5.3 Hz, 1H, H-1), 5.50 (d, *J* = 4.8 Hz, 1H, H-1'), 5.44 (d, *J* = 2.0 Hz, 1H, H-4), 5.27 (dd, *J* = 10.8, 5.4 Hz, 1H, H-2), 5.20 (dd, *J* = 10.9, 2.9 Hz, 1H, H-3), 4.64 (dd, *J* = 7.9, 2.1 Hz, 1H, H-3'), 4.63 – 4.58 (m, *J* = 6.5 Hz, 1H, H-5), 4.31 (dd, *J* = 4.9, 2.3 Hz, 1H, H-2), 4.28 (d, *J* = 8.1 Hz, 1H, H-4'), 4.14 (dd, *J* = 11.1, 6.7 Hz, 1H, H-6$_a$), 4.07 (dd, *J* = 11.2, 6.8 Hz, 1H, H-6$_b$), 3.91 (t, *J* = 6.8 Hz, 1H, H-5), 2.85 – 2.72 (m, 2H, H-6'$_a$ and H-6'$_b$), 2.15 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), 1.51 (s, 3H), 1.43 (s, 3H), 1.36 (s, 3H) and 1.33

(s, 3H) (4×C*H*$_3$ isopropylidene and 4×C*H*$_3$ acetyl).^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.9, 169.9 and 169.6 (4C, 4×*C*OCH_3), 109.2 and 108.5 (2C, 2×C_q isporopylidene), 96.4 (C-1'), 82.9 (C-1), 71.3 (C-4'), 70.8 (C-3'), 70.4 (C-2'), 67.9, 67.7 and 67.6 (3C, C-2, C-3, C-4), 66.6 and 66.5 (2C, C-5, C-5'), 61.2 (C-6), 30.0, 25.9, 25.8, 24.8, 24.3, 20.6, 20.5 and 20.5 (8C, 4×*C*H_3 isopropylidene and 4×*C*H_3 acetyl). Anal. Calcd. for $C_{26}H_{38}O_{14}S$: C, 51.48; H, 6.31; S, 5.29. Found C, 53.78; H, 6.33, S; 5.33.

2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (7).[20] 2-Acetoxy-L-fucal derivative **2** (271 mg, 0.995 mmol), thiol **3** (446 mg, 1.224 mmol, 1.2 equiv.) and DPAP (26 mg, 0.100 mmol, 0.1 equiv.) were dissolved in toluene (7 ml). The reaction mixture was cooled to −85°C (though the mixture is frozen at this temperature, the reaction takes place) and irradiated with UV light. After 15 min the frozen mixture was thawn and DPAP (26 mg, 0.100 mmol, 0.1equiv.) dissolved in toluene (0.5 ml) was added. The mixture was cooled to −85°C and irradiated with UV light. After 15 min DPAP (26 mg, 0.100 mmol, 0.1equiv.) was added as described above and the irradiation continued for another 15 min. When TLC showed almost complete conversion (95:5 CH_2Cl_2–acetone) toluene was evaporated in vacuo. The crude product was chromatographed (85:15 CH_2Cl_2–ethyl acetate, 109 g silica gel) to give 601 mg (95%) of **7** as white foam. Attempt to crystallize the material from common organic solvents failed. R_f 0.6 (95:5CH_2Cl_2–acetone), $[\alpha]_D$ = −150.1 (c = 0.3, $CHCl_3$), (lit.[20] $[\alpha]_D$ = −158.1, c = 0.21, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (d, *J* = 5.6 Hz, 1H, H-1), 5.42 (d, *J* = 1.9 Hz, 1H, H-4'), 5.38 – 5.28 (m, 2H, H-4, H-2), 5.26 (dd, *J* = 10.1, 1.6 Hz, 1H, H-2'), 5.12 (dd, *J* = 10.9, 2.7 Hz, 1H, H-3), 5.07 (dd, *J* = 9.9, 3.3 Hz, 1H, H-3'), 4.67 (d, *J* = 10.2 Hz, 1H, H-1'), 4.37 (q, *J* = 6.3 Hz, 1H, H-5), 4.18 – 4.05 (m, 2H, H-6'$_a$, H-6'$_b$), 3.93 (t, *J* = 6.5 Hz, 1H, H-

5'), 2.18 (s, 3H, COC*H*$_3$), 2.16 (s, 3H, COC*H*$_3$), 2.08 (s, 3H, COC*H*$_3$), 2.07 (s, 3H, COC*H*$_3$), 2.06 (s, 3H, COC*H*$_3$), 1.99 (s, 3H, COC*H*$_3$), 1.99 (s, 3H, COC*H*$_3$), 1.19 (d, *J* = 6.4 Hz, 3H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 170.1, 169.9, 169.8 and 169.2 (7C, 7×*C*OCH$_3$), 81.1 (C-1'), 80.3 (C-1), 74.5 (C-5'), 71.9 (C-3'), 70.5 (C-4), 68.5 (C-3), 67.2 and 67.2 (2C, C-2' and C-4'), 67.0 (C-2), 65.6 (C-5), 61.3 (C-6'), 20.7, 20.6, 20.6, 20.5 and 20.5 (7C, 7×CO*C*H$_3$), 15.8 (C-6); MS (ESI-TOF) *m/z* = 659.046 $[M + Na]^+$. Anal. Calcd. for $C_{26}H_{36}O_{16}S$: C, 49.05; H, 5.70; S, 5.04. Found C, 47.18; H, 5.50; S, 5.01.

1,2:3,4-Di-*O*-isopropylidene-6-*S*-(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-6-thio-α-D-galactopyranose (8). 2-Acetoxy-L-fucal derivative **2** (223 mg, 0.819 mmol), thiol **4** (289 mg 1.046 mmol 1.3 equiv.) and DPAP (21 mg, 0.082 mmol, 0.1 equiv.) were dissolved in toluene (6.5 ml). The reaction mixture was cooled to −85°C and irradiated with UV light (though the mixture is frozen at this temperature, the reaction takes place). After 15 min the frozen mixture was thawn and DPAP (21 mg, 0.082 mmol, 0.1 equiv.) dissolved in toluene (0.5 ml) was added. The mixture was cooled to −85°C and irradiated with UV light. After 15 min DPAP (21 mg, 0.082 mmol, 0.1 equiv.) was added as described above and the irradiation continued for another 15 min. When TLC showed almost complete conversion (7:3 hexane–EtOAc) toluene was evaporated and chromatography (97:3→95:5 CH_2Cl_2–EtOAc, 60 g silica gel) gave 408 mg (91%) of **8** as white foam. R_f 0.3 (7:3 hexane–EtOAc), $[\alpha]_D$ = −193.2 (c = 0.1, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (d, *J* = 5.2 Hz, 1H, H-1), 5.50 (d, *J* = 4.8 Hz, 1H, H-1'), 5.32 – 5.19 (m, 3H, H-4, H-3, H-2), 4.61 (d, *J* = 7.8 Hz, 1H, H-3'), 4.49 (q, *J* = 6.3 Hz, 1H, H-5), 4.32 – 4.25 (m, 2H, H-4', H-2'), 3.86 (t, *J* = 6.9 Hz, 1H, H-5'), 2.82 (dd, *J* = 13.2, 7.2 Hz, 1H, H-6'$_a$), 2.70 (dd, *J* = 13.3, 6.7 Hz, 1H, H-6'$_b$), 2.16 (s, 3H), 2.07 (s, 3H), 1.98 (s, 3H), 1.53 (s, 3H), 1.44 (s,

3H), 1.35 (s, 3H) and 1.33 (s, 3H) (4×C*H*$_3$ isopropylidene and 3×C*H*$_3$ acetyl), 1.16 (d, *J* = 6.5 Hz, 3H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 170.0 and 169.8 (3C, 3×*C*OCH_3), 109.3 and 108.6 (2C, 2×C_q isporopylidene), 96.5 (C-1'), 82.3 (C-1), 71.7 (C-4'), 70.9, 70.9, 70.4, 68.5, 68.1 and 67.8 (6C, C-5', C-4, C-3, C-3', C-2, C-2'), 64.8 (C-5'), 28.8 (C-6'), 26.1, 26.0, 24.9, 24.5, 20.8, 20.6 and 20.6 (7C, 4×*C*H_3 isopropylidene and 3×*C*H_3 acetyl), 15.9 (C-6); MS (ESI-TOF) *m/z* = 571.132 $[M + Na]^+$. Anal. Calcd for $C_{24}H_{36}O_{12}S$: C, 52.54; H, 6.61; S 5.84. Found C, 51.08; H, 6.44; S 5.95.

Acknowledgments

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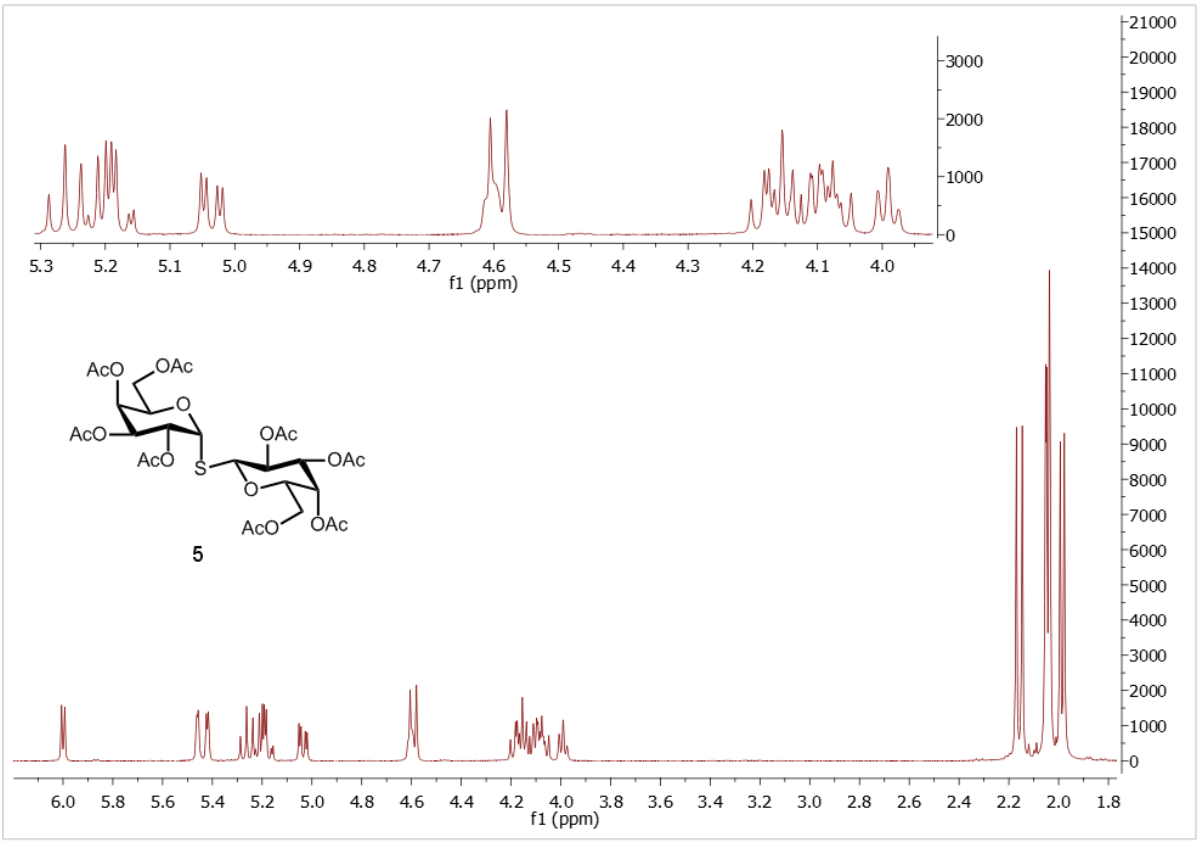
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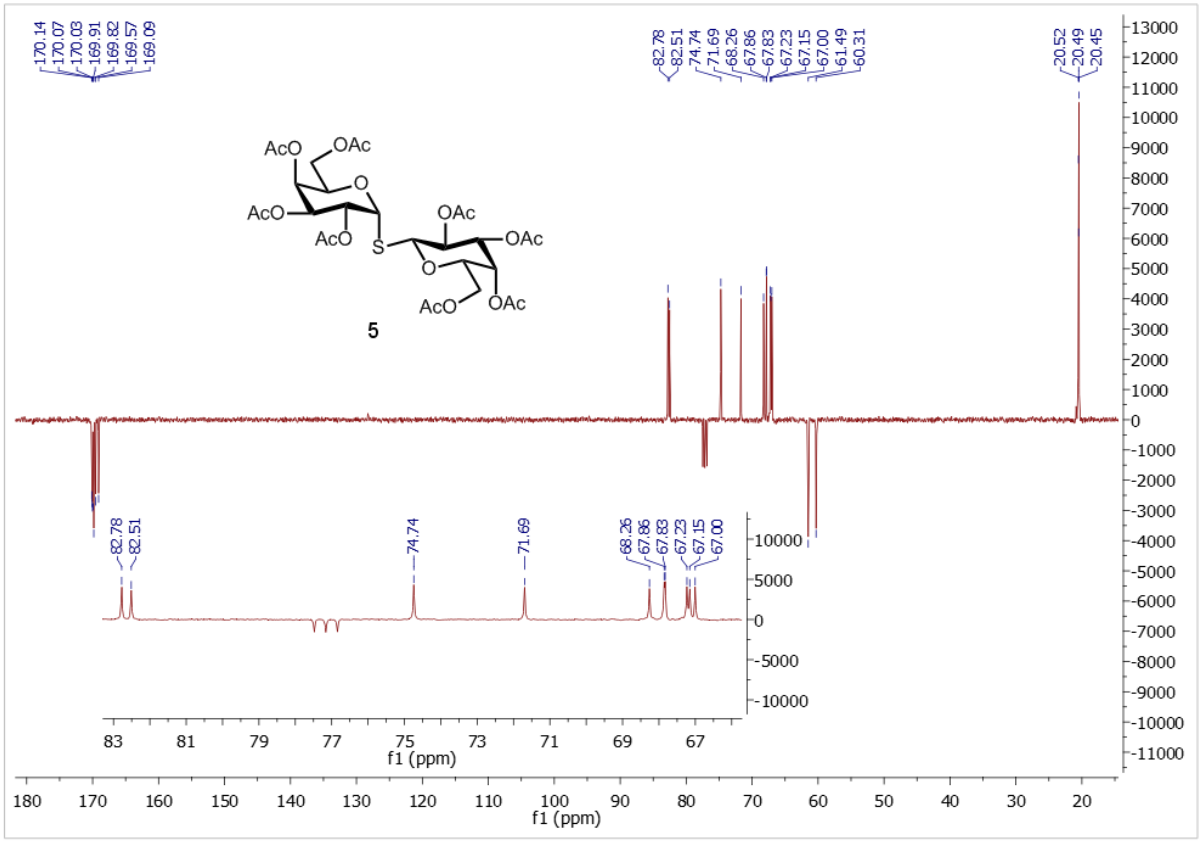
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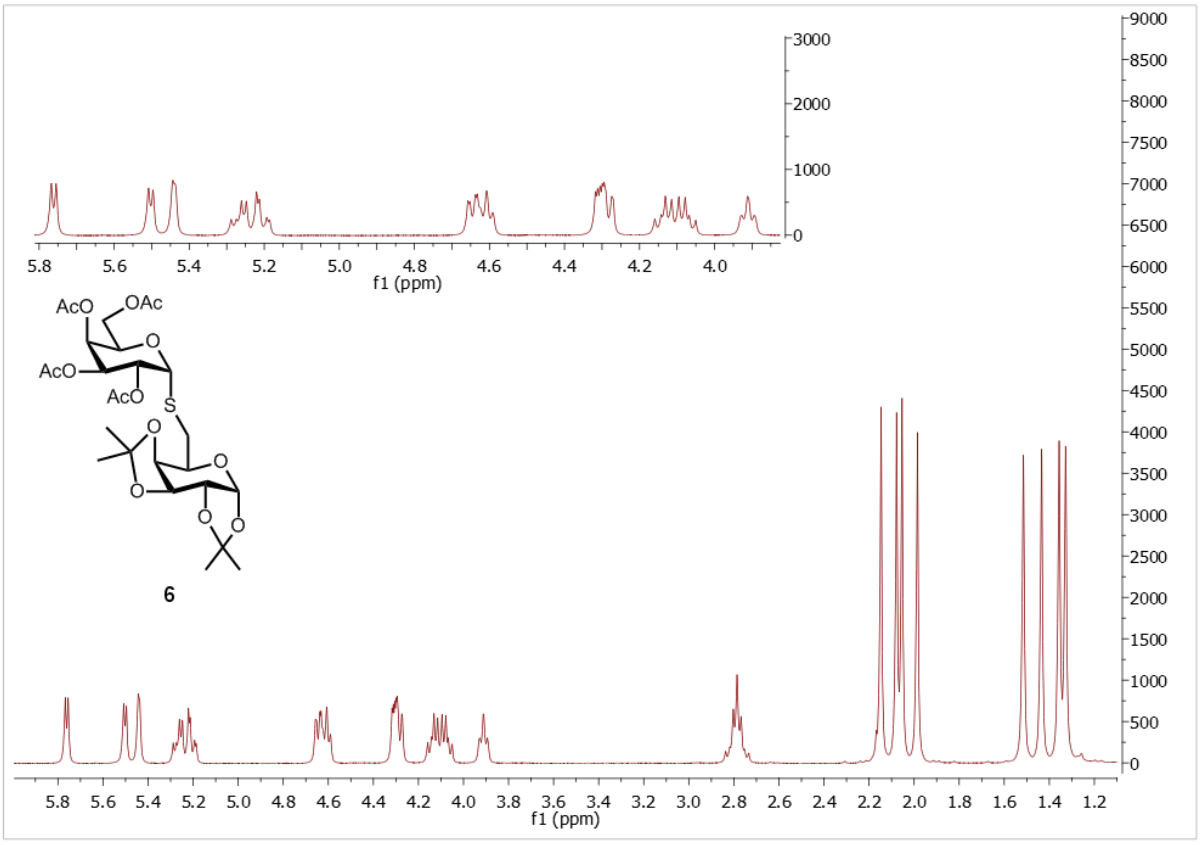
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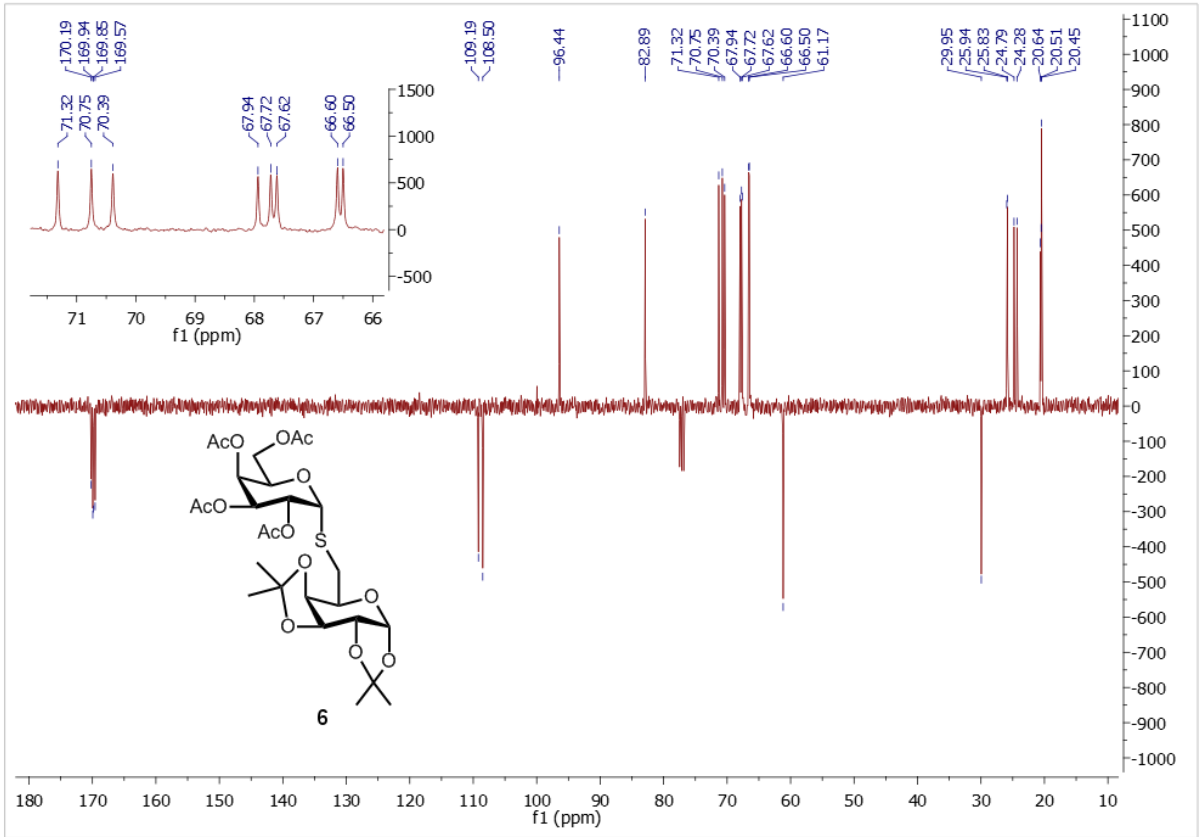
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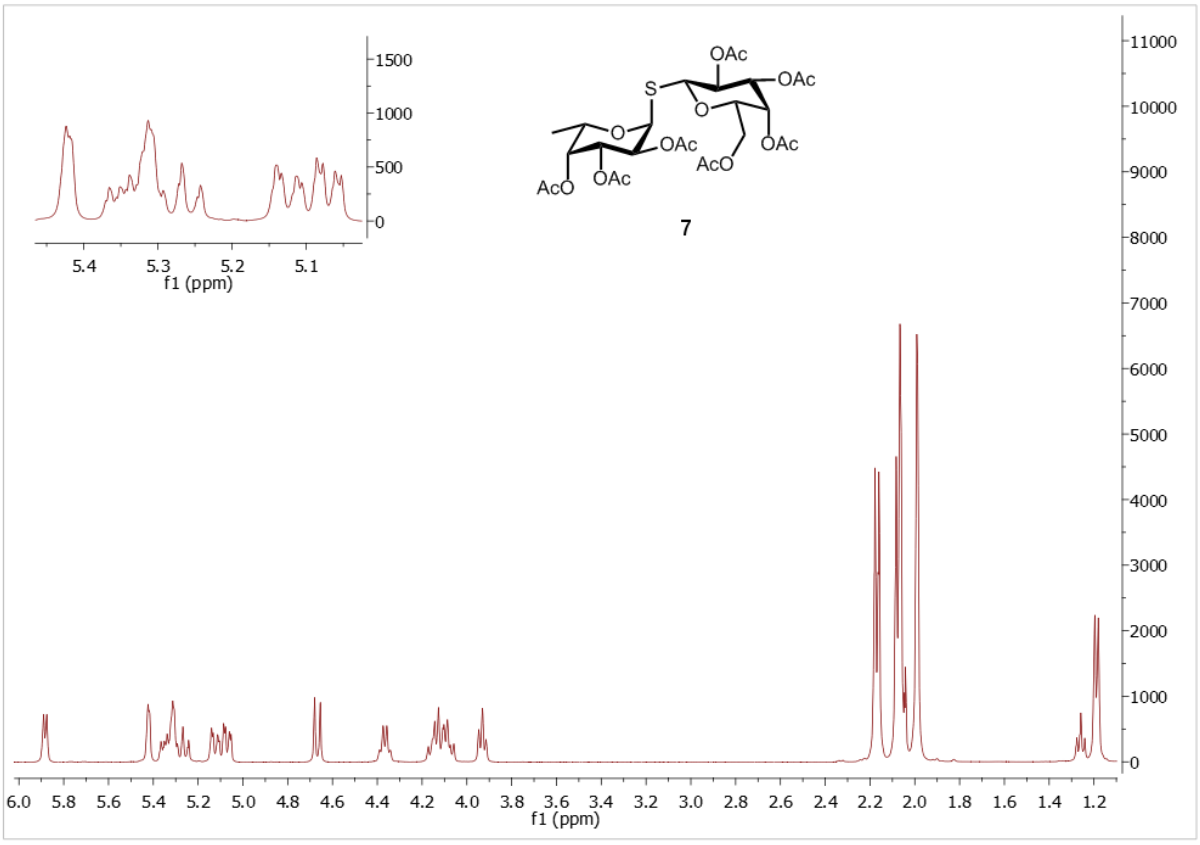
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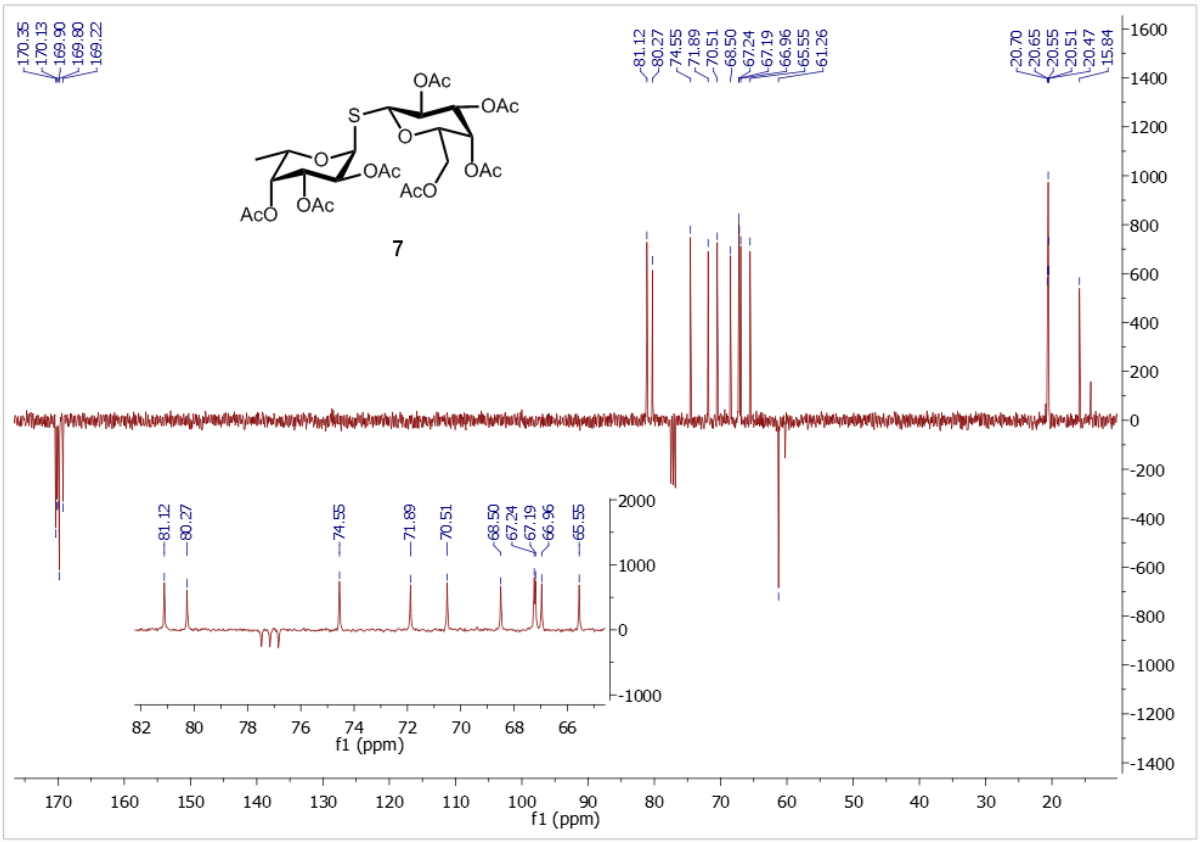
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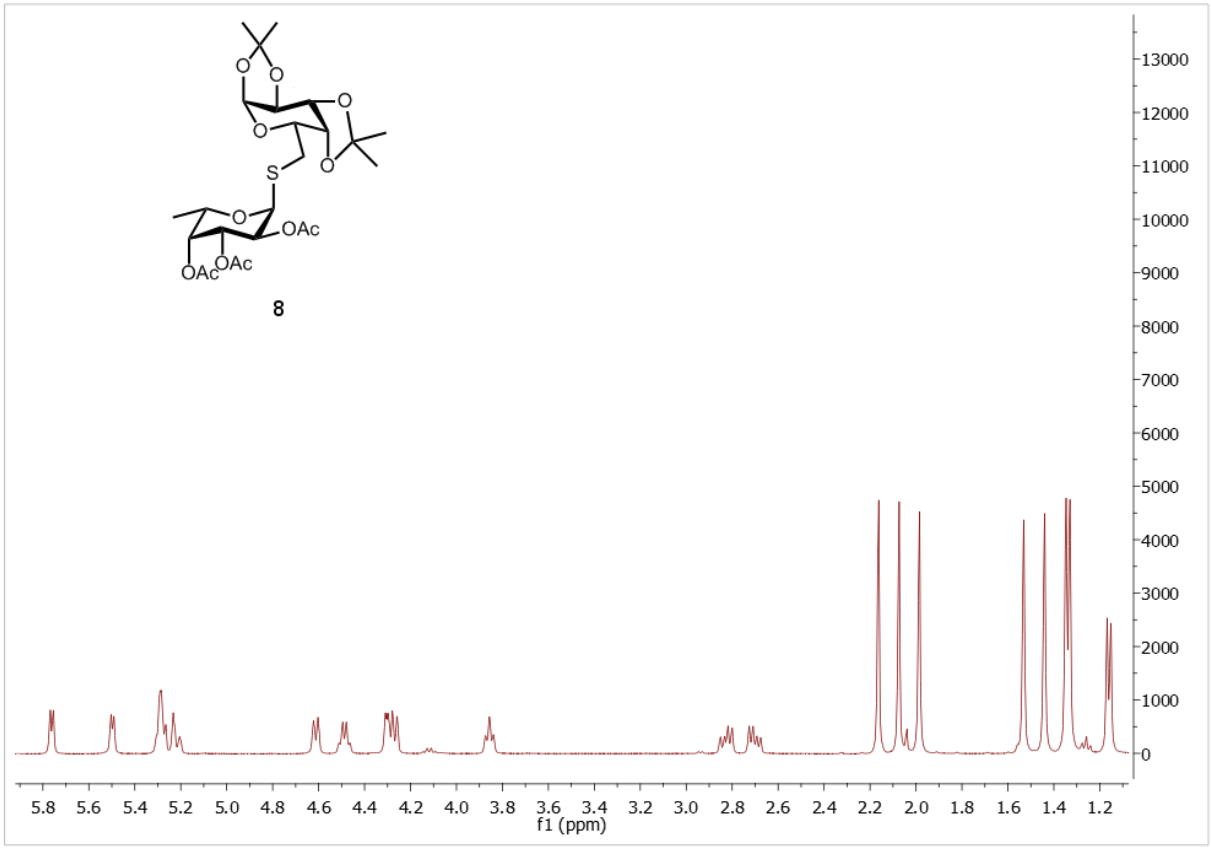
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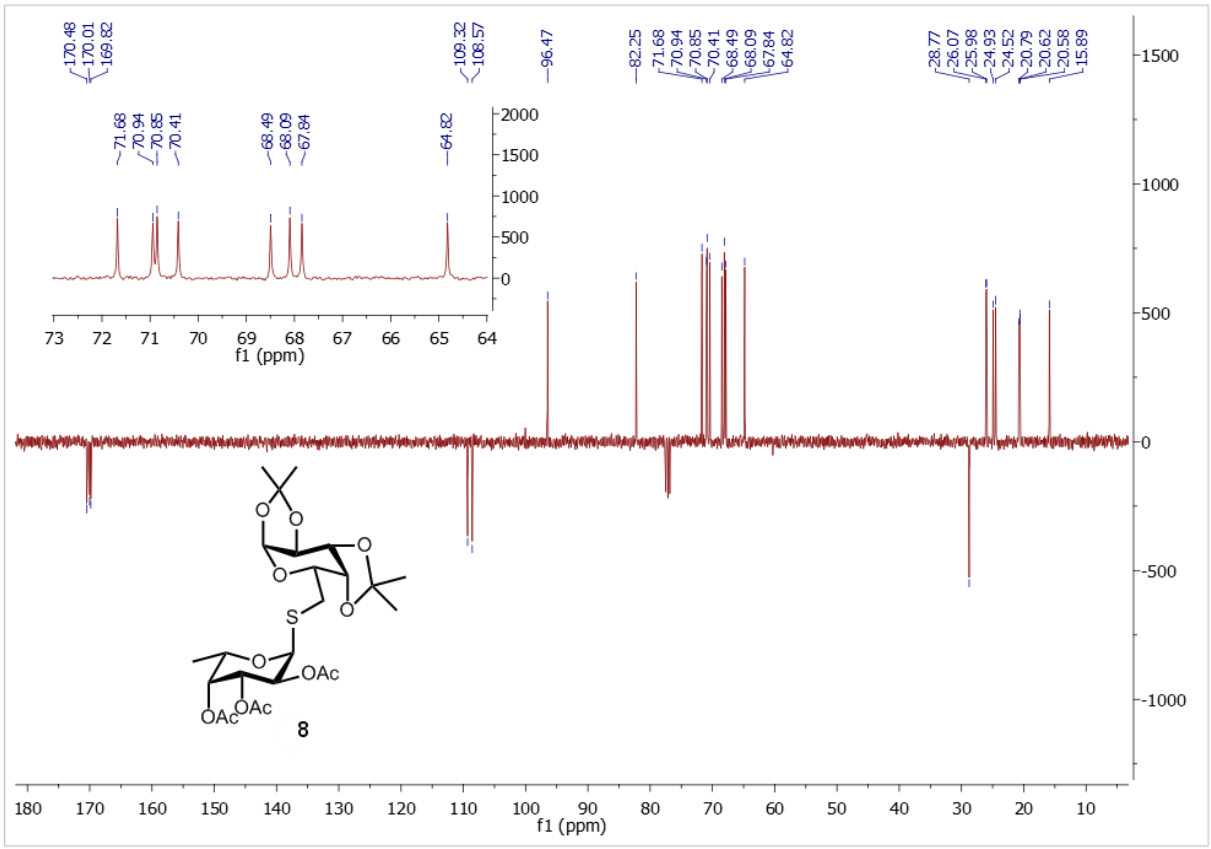
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